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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,166	04/04/2001	Frederique Ahne Le Gal	102.174	2214

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,166	LE GAL ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25,26,28-31,35-39,41 and 43* is/are pending in the application.

4a) Of the above claim(s) *28,29,31,39 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25,26,30,35-38 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JC

DETAILED ACTION

1. Applicant's amendment filed 12/21/04 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 23-40 and 43), and species of dipalmitoyl lysyl as the lipid moiety, TT 830-843 as the T cell epitope, amino acid residues 20-34 of SEQ ID NO: 276 as the CTL epitope, i.e., FPVTPQVPLRPMTYK, and the spacer RGR in Applicant's reply filed 1/6/04.

Claims 23, 25, 26, 30, 35-38 and 43 are currently being examined.

The following objections remain.

3. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the brief description of the drawings for Fig. 5, i.e., Figure 5 discloses two peptide sequences).

4. The disclosure is objected to because of the following informalities:

a. The brief description of the drawings for Fig. 6 should be Fig. 6 A-C.

b. The use of the trademarks VYDAC (page 11 at line 18), ZORBAX (page 11 at line 18) and ELISPOT(the Examiner noted one occurrence of lower case letters, please search for and correct) have been noted in this application. They should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

The following are new grounds of rejection necessitated by Applicant's amendment filed 12/21/04.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 23, 25, 26, 30, 36-38 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed lipopeptide and vaccine thereof, recited in the instant claims.

The instant claims encompass a lipopeptide comprising "one lipid moiety" and "at least one CTL epitope consists of a CTL epitope of a HIV protein", "at least one auxiliary T epitope" and spacer(s), and a vaccine comprising said lipopeptide. There is insufficient disclosure in the specification on such a lipopeptide and vaccine comprising said lipopeptide.

The specification discloses that the lipid portion of the lipopeptide can comprise one or several optionally branched or [u]insaturated chains derived from C10-C20 fatty acids or a steroid derivative, and that it may also be made of or comprise a moiety of palmitic, oleic, linoleic, linolenic, 2-aminohexadecanoic acids, pimeluatide or trimexautide (especially page 5 at lines 19-32). The specification discloses that the lipid portion may be made of or comprise a moiety of palmitic, oleic, linoleic, linolenic, 2-aminohexadecanoic acids, pimelautide or trimexautide (especially page 5 at lines 30-32).

The specification does not disclose any lipopeptide used prophylactically as a vaccine.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any lipid or portion thereof. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

7. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a lipopeptide and vaccine thereof, comprising "one lipid moiety" and "at least one CTL epitope consists of a CTL epitope of a HIV protein", "at least one auxiliary T epitope" and spacer(s), and a vaccine comprising said lipopeptide, and wherein the vaccine is used for prophylaxis. The specification has not enabled the breadth of the claimed invention because the claims encompass lipopeptides comprising any lipid or portion thereof, and use prophylactically as a vaccine. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed lipopeptide/composition thereof can be made and used prophylactically. The specification discloses no working examples with regards to the use of the instant invention for prevention of disease in vivo, specifically for prevention of HIV.

The disclosed use for the claimed lipopeptide/vaccine thereof is for the production of a medicine or a vaccine effective as a preventative or a curative by means of in vivo generation of CTL (page 1 at lines 14-15 and page 7 at lines 5-19).

The specification discloses that the lipid portion of the lipopeptide can comprise one or several optionally branched or [u]insaturated chains derived from C10-C20 fatty acids or a steroid, linolenic, 2-aminohexadecanoic acids, pimeluatide or trimexautide (especially page 5 at lines 19-32). The specification discloses that the lipid portion may be made of or comprise a moiety of palmitic, oleic, linoleic, linolenic, 2-aminohexadecanoic acids, pimelautide or trimexautide (especially page 5 at lines 30-32).

The specification does not disclose any lipopeptide used prophylactically as a vaccine.

Evidentiary reference the Merck Manual (of record) teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease. Evidentiary reference Encyclopedia Brittanica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Base claim 23 is indefinite in the recitation of "said amino acids being independently selected from" because it is not clear what is meant. It is suggested that In addition, the recited limitation "hydrophilic aminoacid spacer chain" must necessarily include charged amino acid residues, and it is not clear from the recitation of "being independently selected from glycine, arginine, glutamic acid, asparatic acid and cysteine" if all of the recited amino acid residues must comprise the chain or if just one may comprise the chain, i.e., glycine and cysteine are non-charged amino acid residues, and hence they would not make a hydrophilic spacer chain.

b. Base claim 23 is indefinite because the period at the end of the said claim has been deleted.

c. Claim 25 is indefinite in the recitation of "wherein at least one of the amino acid spacer chains is least one member of the group consisting of 1 to 10 glycines and arginines" because it is not clear what is meant. It is not clear if the at least one spacer chain is 1 to 10 glycines *or* arginines, or if the at least one spacer chain may be a mixture of between 1 to 10 glycines *and* arginines. In addition, it is suggested that Applicant amend said claim to recite "at least one member".

d. Claim 38 is indefinite in the recitation of "titanic" in line 2 because it is not clear what is meant. It is suggested that Applicant amend said claim to recite "tetanus".

e. Base claim 23 is indefinite in the recitation of "aminoacids" and "aminoacid" because it is not clear what is meant. It is suggested that Applicant amend said claim to recite "amino acid residues" and "amino acid residue" if that is what is meant. In addition, "asparatic acid" is misspelled. It is suggested that Applicant amend said claim to recite "aspartic acid" if that is what is meant.

10. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the 371 application, i.e., 4/6/99, as an English language translation of the foreign priority document FR 98 04323 filed 4/7/98 has not been provided.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 in view of EP 0346022A1, Rammensee et al (Immunogenetics 1995, 41: 178-228), BenMohamed et al (Eur. J. Immunology 1997, 27(5): 1242-1253), U.S. Patent No. 5,935,824 (of record), US2003/0162719A1 (of record) and Alberts et al (Molec. Biol. Cell, 2nd ed, 1989, page 54, previously provided).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-842 QYIKANSKFIGITE to CTL epitopes will also increase immunogenicity, and (3)teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th

epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain, said amino acid residues being independently selected from glutamic acid, aspartic acid and cysteine, as well as from glycine and arginine.

EP 0346022A1 teaches an HLA-B27 restricted CTL epitope containing peptide from HIV (gag p24 265-274, KRWIILGLNKIVRMY) that can be incorporated into a vaccine against HIV, either alone or in the form of a fusion protein containing other epitopes (entire article, especially abstract, summary of the invention and claims).

Rammensee et al teach the minimal CTL epitope HIV-1 gag p24 265-274 (i.e., KRWIILGLNK, a subsequence of that taught by EP 0346022A1 above), as well as other HIV epitopes restricted by HLA-B27 as well as by other class I molecules (especially Table 3 on page 200, page 209, page 210, pages 193-198).

BenMohamed et al teach that incorporating a simple palmitoyl-lysine chain in a peptide from an infectious agent that contains Th and CTL epitopes can dramatically increase Th and CTL responses.

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

US 2003/0162719A1 discloses that peptides such as class I MHC antigens and class II MHC antigens are particularly intractable to transmembrane transport, and that polymers of highly basics subunits such as Arg attached to the peptide can facilitate transport across the cell membrane of an antigen presenting cell (APC) in order to promote or elicit an immune response, and further discloses a poly-L arginine linker of formula $CAAA(R)_7$, the " C" being useful when the product is coupled via crosslinking rather than made by recombinant means (especially column 1 at [0004], [0009], [0013], [0019][0051], [0087], [0144], [0216]). US 2003/0162719A1 discloses that the peptides linked to the basic transporting polymers can be produced by using a synthesizer or by recombinant methods (especially [0145]).

Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an HIV CTL epitope as taught by US Patent No. 5,935,824 and by Rammensee et al in place of the CTL epitope in the peptide taught by WO 95/19783 A1 comprising a palmitic acid moiety and to have used a hydrophilic spacer comprising either Lys or Arg as disclosed by US Patent No. 5,935,824 and by US 2003/0162719A1 (including the species of $CAAA(R)_7$, including minus the Cys residue, and including the Gly taught by WO 95/19783 A1) between the Th and the CTL epitope and in between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1 and to have made a vaccine as taught by EP 0346022A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to improve the efficiency of immunization of the HIV CTL epitope taught by Rammensee et al and by EP 0346022A1 by using a lipopeptide such as the one taught by WO 95/19783 A1 but with the said HIV CTL epitope, since WO 95/19783 A1 teaches that adding a multivalent auxiliary Th epitope and a lipid such as palmitic acid increases immunogenicity, and BenMohammed et al teach that use of a single palmitoyl chain can dramatically increase immune response to a peptide containing T and B cell epitopes, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, i.e., will be cleaved, and US 2003/0162719A1 discloses that the transport of peptides such as class I and class II MCH antigens, i.e., CTL and HTL epitopes, respectively, across APC cell membranes is enhanced by attachment to polymers of basic subunits such as Arg, WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other, and Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the solubility of the lipopeptide in solution because the lipid moiety is hydrophobic as was known to one of ordinary skill in the art at the time the invention was made. Claim 26 is included in this rejection because Gly and Arg are two amino acid residues from which the 2 to 10 amino acid residue linkers may be comprised.

13. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 in view of EP 0346022A1, Rammensee et al (Immunogenetics 1995, 41: 178-228), U.S. Patent No. 5,935,824 (of record), US2003/0162719A1 (of record) and Alberts et al (Molec. Biol. Cell, 2nd ed, 1989, page 54, previously provided).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-842 QYIKANSKFIGITE to CTL epitopes will also increase immunogenicity, and (3)teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain, said amino acid residues being independently selected from glutamic acid, aspartic acid and cysteine, as well as from glycine and arginine.

EP 0346022A1 teaches an HLA-B27 restricted CTL epitope containing peptide from HIV (gag p24 265-274, KRWIILGLNKIVRMY) that can be incorporated into a vaccine against HIV, either alone or in the form of a fusion protein containing other epitopes (entire article, especially abstract, summary of the invention and claims).

Rammensee et al teach the minimal CTL epitope HIV-1 gag p24 265-274 (i.e., KRWIILGLNK, a subsequence of that taught by EP 0346022A1 above), as well as other HIV epitopes restricted by HLA-B27 as well as by other class I molecules (especially Table 3 on page 200, page 209, page 210, pages 193-198).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

US 2003/0162719A1 discloses that peptides such as class I MHC antigens and class II MHC antigens are particularly intractable to transmembrane transport, and that polymers of highly basics subunits such as Arg attached to the peptide can facilitate transport across the cell membrane of an antigen presenting cell (APC) in order to promote or elicit an immune response, and further discloses a poly-L arginine linker of formula $CAAA(R)_7$, the " C" being useful when the product is coupled via crosslinking rather than made by recombinant means (especially column 1 at [0004], [0009], [0013], [0019][0051], [0087], [0144], [0216]). US 2003/0162719A1 discloses that the peptides linked to the basic transporting polymers can be produced by using a synthesizer or by recombinant methods (especially [0145]).

Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an HIV CTL epitope as taught by US Patent No. 5,935,824 and by Rammensee et al in place of the CTL epitope in the peptide taught by WO 95/19783 A1 comprising a palmitic acid moiety and to have used a hydrophilic spacer comprising either Lys or Arg as disclosed by US Patent No. 5,935,824 and by US 2003/0162719A1 (including the species of $CAAA(R)_7$, including minus the Cys residue, and including the Gly taught by WO 95/19783 A1) between the Th and the CTL epitope and in between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1 and to have made a vaccine as taught by EP 0346022A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to improve the efficiency of immunization of the HIV CTL epitope taught by Rammensee et al and by EP 0346022A1 by using a lipopeptide such as the one taught by WO 95/19783 A1 but with the said HIV CTL epitope, since WO 95/19783 A1 teaches that adding a multivalent auxiliary Th epitope and a lipid such as palmitic acid increases immunogenicity, and Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, i.e., will be cleaved, and US 2003/0162719A1 discloses that the transport of peptides such as class I and class II MCH antigens, i.e., CTL and HTL epitopes, respectively, across APC cell membranes is enhanced by attachment to polymers of basic subunits such as Arg, WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other, and Alberts et al

teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the solubility of the lipopeptide in solution because the lipid moiety is hydrophobic as was known to one of ordinary skill in the art at the time the invention was made. Claim 26 is included in this rejection because Gly and Arg are two amino acid residues from which the 2 to 10 amino acid residue linkers may be comprised.

14. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 in view of Deprez et al (Vaccine, 1996, 14(5): 375-382), Berzofsky et al (J. Clin. Invest., 1991, 88: 876-884), EP 0346022A1, Rammensee et al (Immunogenetics 1995, 41: 178-228), U.S. Patent No. 5,935,824 (of record), US2003/0162719A1 (of record) and Alberts et al (Molec. Biol. Cell, 2nd ed. 1989, page 54, previously provided).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-842 QYIKANSKFIGITE, which is recognized by Th cells in the majority of the population, to CTL epitopes will also increase immunogenicity, and (3)teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain, said amino acid residues being independently selected from glutamic acid, aspartic acid and cysteine, as well as from glycine and arginine.

Deprez et al teach HIV env peptides that contain class I and class II epitopes, i.e., CTL and antibody epitopes, linked to trimexautide or palmitic acid or dexadecanoic acid or cholesterol, i.e., single lipid moieties. Deprez et al further teach a 41-mer chimeric lipopeptide made by collinear synthesis of three sequences from influenza NP protein containing three CTL epitopes. Deprez et al teach that each epitope was restricted to a different haplotype, i.e., to a different class I MHC molecule, and that provided a concomitant stimulation of specific Th cell responses were achieved, a CTL response could be elicited to all three epitopes (see entire article, especially, abstract, introduction, peptide synthesis section of materials and methods, figure 1, discussion).

Berzofsky et al teach construction of peptides encompassing multideterminant clusters of HIV env protein (i.e., large peptide subsequences of HIV env protein that contain overlapping or contiguous CTL epitopes restricted by different HLA or MHC class I molecules) to induce in vitro T cell responses in mice and humans of multiple MHC types. Berzofsky et al teach that these peptides may be useful components of a vaccine due to their broad recognition by from 52-73% of outbred, HLA-diverse infected human donors. Berzofsky et al teach that these peptides by themselves do not constitute a complete vaccine, and that vaccines are known to elicit antibodies and Th cells as well as CTL, that it is desirable that a synthetic vaccine elicit all three major arms of the immune response (especially abstract, introduction, discussion).

EP 0346022A1 teaches an HLA-B27 restricted CTL epitope containing peptide from HIV (gag p24 265-274, KRWIILGLNKIVRMY) that can be incorporated into a vaccine against HIV, either alone or in the form of a fusion protein containing other epitopes (entire article, especially abstract, summary of the invention and claims).

Rammensee et al teach the minimal CTL epitope HIV-1 gag p24 265-274 (i.e., KRWIILGLNK, a subsequence of that taught by EP 0346022A1 above), as well as other HIV epitopes restricted by HLA-B27 as well as by other class I molecules. Rammensee et al further teach peptides that overlap with KRWILLGLNK that are also CTL epitopes that are restricted by HLA-B8, i.e., EIYKRWIIL and GEIYKRWIL (especially Table 3 on page 200, page 209, page 210, pages 193-198).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

US 2003/0162719A1 discloses that peptides such as class I MHC antigens and class II MHC antigens are particularly intractable to transmembrane transport, and that polymers of highly basics subunits such as Arg attached to the peptide can facilitate transport across the cell membrane of an antigen presenting cell (APC) in order to promote or elicit an immune response, and further discloses a poly-L arginine linker of formula $CAAA(R)_7$, the " C" being useful when the product is coupled via crosslinking rather than made by recombinant means (especially column 1 at [0004], [0009], [0013], [0019][0051], [0087], [0144], [0216]). US 2003/0162719A1 discloses that the peptides linked to the basic transporting polymers can be produced by using a synthesizer or by recombinant methods (especially [0145]).

Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the lipopeptide taught by WO 95/19783 A1 by using an HIV CTL epitope such as that taught by US Patent No. 5,935,824 or by Rammensee et al or by EP 0346022A1 for the antigenic determinant from viral protein, or to have used a cluster peptide constructed using knowledge of the overlapping HIV CTL epitope peptides taught by Rammensee et al (i.e., one comprising GEIYKRWIILGLNK) as per the teaching of Berzofsky et al, to have retained the auxiliary Th epitope taught by WO 95/19783 A1 that is recognized by Th cells in the majority of the population, to have used the palmitic acid moiety taught by WO 95/19783 A1 or Deprez et al or one of the other single lipid moieties taught by Deprez et al, to have used a hydrophilic spacer comprising either Lys or Arg as disclosed by US Patent No. 5,935,824 and by US 2003/0162719A1 (including the species of $CAAA(R)_7$, including minus the Cys residue, and including the Gly taught by WO 95/19783 A1) between the Th and the CTL epitope and in between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1, and to have made a vaccine as taught by EP 0346022A1 or by Berzofsky et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to elicit an immune response or to improve efficacy of immunization to HIV, because WO 95/19783 A1 and Deprez et al teach attachment of a single lipid moiety can enhance the immune response to a CTL epitope, WO 95/19783 A1, Deprez et al and Berzofsky et al teach that the use of Th epitope in combination with a CTL epitope can also enhance elicitation of the immune response and that the elicitation of antibodies and Th cells is desirable in a vaccine composition, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, i.e., will be cleaved, US 2003/0162719A1 discloses that the transport of peptides such as class I and class II MCH antigens, i.e., CTL and HTL epitopes, respectively, across APC cell membranes is enhanced by attachment to polymers of basic subunits such as Arg, WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other, and Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its

positive charge is stabilized by resonance. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the solubility of the lipopeptide in solution because the lipid moiety is hydrophobic as was known to one of ordinary skill in the art at the time the invention was made. In the case of the cluster peptide, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a vaccine that would be broadly reactive in the population as taught by Berzofsky et al because Berzofsky et al teach a vaccine comprising a cluster peptide can be broadly reactive in diverse outbred populations such as humans, and that a complete synthetic vaccine should elicit not only CTL, but Th cells and antibodies. Claim 26 is included in this rejection because Gly and Arg are two amino acid residues from which the 2 to 10 amino acid residue linkers may be comprised.

15. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 in view of U.S. Patent No. 5,993,823, U.S. Patent No. 5,935,824 (of record), US2003/0162719A1 (of record) and Alberts et al (Molec. Biol. Cell, 2nd ed, 1989, page 54, previously provided).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-842 QYIKANSKFIGITE, which is recognized by Th cells in the majority of the population, to CTL epitopes will also increase immunogenicity, and (3)teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical

composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain, said amino acid residues being independently selected from glutamic acid, aspartic acid and cysteine, as well as from glycine and arginine.

U.S. Patent No. 5,993,823 discloses that lipopeptides/vaccine compositions thereof can comprise a single lipid moiety, palmitic acid, trimexautide or cholsterol, and a sequence of between 10 and 40 amino acid residues approximately and comprising a CTL epitope from HIV, such as for example, HIV env 312-327 or 302-335. U.S. Patent No. 5,993,823 discloses that neutralizing antibodies have been obtained in mice by immunization against HIV env derived lipopeptides. U.S. Patent No. 5,993,823 further discloses that lipopeptide vaccines are safe, without side effects and easily applicable to humans. U.S. Patent No. 5,993,823 discloses association of lipopeptides inducing CTL to other lipopeptides capable to generate antibodies should result in efficient protection. U.S. Patent No. 5,993,823 discloses CTL epitope from a tumor specific protein collinear with the promiscuous (i.e., multivalent auxiliary Th epitope) Th sequence KSSQYIKANSKFIGITE. U.S. Patent No. 5,993,823 discloses using the lipopeptides to treat warm-blooded animals, including humans to elicit CTL against viral or tumor proteins (see entire document, especially abstract, column 2 at lines 59-67, column 3-7 at line 18, column 46 at conclusion and claims).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

US 2003/0162719A1 discloses that peptides such as class I MHC antigens and class II MHC antigens are particularly intractable to transmembrane transport, and that polymers of highly basics subunits such as Arg attached to the peptide can facilitate transport across the cell membrane of an antigen presenting cell (APC) in order to promote or elicit an immune response, and further discloses a poly-L arginine linker of formula $CAAA(R)_7$, the " C" being useful when the product is coupled via crosslinking rather than made by recombinant means (especially column 1 at [0004], [0009], [0013], [0019][0051], [0087], [0144], [0216]). US 2003/0162719A1 discloses that the peptides

linked to the basic transporting polymers can be produced by using a synthesizer or by recombinant methods (especially [0145]).

Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the lipopeptide taught by WO 95/19783 A1 by using an HIV CTL epitope such as that taught by US Patent No. 5,935,824 or as disclosed by U.S. Patent No. 5,993,823 for the antigenic determinant from viral protein, to have retained the multivalent auxiliary Th epitope taught by WO 95/19783 A1 or disclosed by U.S. Patent No. 5,993,823, to have used the palmitic acid moiety taught by WO 95/19783 A1 or disclosed by U.S. Patent No. 5,993,823 or one of the other single lipid moieties disclosed by U.S. Patent No. 5,993,823, to have used a hydrophilic spacer comprising either Lys or Arg as disclosed by US Patent No. 5,935,824 and by US 2003/0162719A1 (including the species of $CAAA(R)_7$, including minus the Cys residue, and including the Gly taught by WO 95/19783 A1) between the Th and the CTL epitope and in between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1 and to have made a vaccine as disclosed by U.S. Patent No. 5,993,823.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to elicit an immune response or to improve efficacy of immunization to HIV, because WO 95/19783 A1 and U.S. Patent No. 5,993,823 teach attachment of a single lipid moiety can enhance the immune response to a CTL epitope, WO 95/19783 A1 and U.S. Patent No. 5,993,823 teach that the use of Th epitope in combination with a CTL epitope to enhance elicitation of the immune response, and that the elicitation of antibodies and Th cells is desirable in a vaccine composition, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, i.e., will be cleaved, US 2003/0162719A1 discloses that the transport of peptides such as class I and class II MCH antigens, i.e., CTL and HTL epitopes, respectively, across APC cell membranes is enhanced by attachment to polymers of basic subunits such as Arg, WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other, and Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance. Claim 26 is included in this rejection because Gly and Arg are two amino acid residues from which the 2 to 10 amino acid residue linkers may be comprised.

16. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 in view of U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564, and further in view of U.S. Patent No. 5,935,824 (of record), US2003/0162719A1 (of record) and Alberts et al (Molec. Biol. Cell, 2nd ed, 1989, page 54, previously provided).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-842 QYIKANSKFIGITE, which is recognized by Th cells in the majority of the population, to CTL epitopes will also increase immunogenicity, and (3) teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain, said amino acid residues being independently selected from glutamic acid, aspartic acid and cysteine, as well as from glycine and arginine.

U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 discloses that lipopeptides/vaccine compositions thereof can comprise a single lipid moiety, palmitic acid, trimexautide or cholsterol, and a sequence of between 10 and 40 amino acid residues approximately and comprising a CTL epitope from HIV, such as for example, HIV env 312-327 or 302-335. U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 discloses that neutralizing antibodies have been obtained in mice by immunization against HIV env derived lipopeptides. U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 discloses that lipopeptide vaccines are safe, without side effects and easily applicable to humans. U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 discloses discloses association of lipopeptides inducing CTL to other lipopeptides capable to generate antibodies should result in efficient protection.
U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 discloses using the lipopeptides as vaccines to elicit CTL against viral or tumor proteins (U.S. Patent No. 5,871,746 see entire document, especially abstract, column 2 at lines 59-67, column 3-7 at line 40, column 28 at lines 17-30 and claims; U.S. Patent No. 6,015,564 see entire document especially abstract, paragraph spanning columns 2 and 3, columns 3-8 and the top of column 9, column 30 at the last paragraph and claims).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

US 2003/0162719A1 discloses that peptides such as class I MHC antigens and class II MHC antigens are particularly intractable to transmembrane transport, and that polymers of highly basics subunits such as Arg attached to the peptide can facilitate transport across the cell membrane of an antigen presenting cell (APC) in order to promote or elicit an immune response, and further discloses a poly-L arginine linker of formula $CAAA(R)_7$, the " C" being useful when the product is coupled via crosslinking rather than made by recombinant means (especially column 1 at [0004], [0009], [0013], [0019][0051], [0087], [0144], [0216]). US 2003/0162719A1 discloses that the peptides linked to the basic transporting polymers can be produced by using a synthesizer or by recombinant methods (especially [0145]).

Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the lipopeptide taught by WO 95/19783 A1 by using an HIV CTL epitope such as that disclosed by U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 for the antigenic determinant from viral protein, to have retained the multivalent auxiliary Th epitope taught by WO 95/19783 A1, to have used the palmitic acid moiety taught by WO 95/19783 A1 or disclosed by U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 one of the other single lipid moieties disclosed by U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564, to have used a hydrophilic spacer comprising either Lys or Arg as disclosed by US Patent No. 5,935,824 and by US 2003/0162719A1 (including the species of $CAAA(R)_7$, including minus the Cys residue, and including the Gly taught by WO 95/19783 A1) between the Th and the CTL epitope and in between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1 and to have made a vaccine as disclosed by U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to elicit an immune response or to improve efficacy of immunization to HIV, because WO 95/19783 A1 and U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 teach attachment of a single lipid moiety can enhance the immune response to a CTL epitope, WO 95/19783 A1 teaches and U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 discloses the use of a Th epitope in combination with a CTL epitope to enhance elicitation of the immune response, and that the elicitation of antibodies and Th cells is desirable in a vaccine composition, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, i.e., will be cleaved, US 2003/0162719A1 discloses that the transport of peptides such as class I and class II MCH antigens, i.e., CTL and HTL epitopes, respectively, across APC cell membranes is enhanced by attachment to polymers of basic subunits such as Arg, WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other, and Alberts et al teach that the $C=NH2^+$ group of arginine is very basic because its positive charge is stabilized by resonance. Claim 26 is included in this rejection because Gly and Arg are two amino acid residues from which the 2 to 10 amino acid residue linkers may be comprised.

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 23, 25, 26, 30, 35-38 and 43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4-9 of U.S. Patent No. 5,871,746 or U.S. Patent No. 6,015,564 in view of WO 95/19783 A1, U.S. Patent No. 5,935,824 (of record), US2003/0162719A1 (of record) and U.S. Patent No.5,993,823.

Claims 1 and 4-9 of '746 or '564 are drawn to a lipopeptide comprising a peptide having between 10 and 40 amino acid residues and at least one antigenic determinant such as the HIV determinants recited in claims 4-6, and comprising at least one chain derived from the lipid moiety species recited in claims 1 and 7-9.

Claims 1 and 4-9 of '746 or '564 do not recite the at least one auxiliary T epitope and the hydrophilic spacer chain(s), nor the vaccine recited in instant claims 23, 25, 26, 30, 35-38 and 43.

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-842 QYIKANSKFIGITE, which is recognized by Th cells in the majority of the population, to CTL epitopes will also increase immunogenicity, and (3)teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide

or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

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U.S. Patent No. 5,993,823 discloses that lipopeptides/vaccine compositions thereof can comprise a single lipid moiety, palmitic acid (including N or ε or lysylamide), trimexautide or cholsterol, and a sequence of between 10 and 40 amino acid residues approximately and comprising a CTL epitope from HIV, such as for example, HIV env 312-327 or 302-335. U.S. Patent No. 5,993,823 discloses that neutralizing antibodies have been obtained in mice by immunization against HIV env derived lipopeptides. U.S. Patent No. 5,993,823 further discloses that lipopeptide vaccines are safe, without side effects and easily applicable to humans. U.S. Patent No. 5,993,823 discloses association of lipopeptides inducing CTL to other lipopeptides capable to generate antibodies should result in efficient protection. U.S. Patent No. 5,993,823 discloses CTL epitope from a tumor specific protein collinear with the promiscuous (i.e., multivalent auxiliary Th epitope) Th sequence KSSQYIKANSKFIGITE. U.S. Patent No. 5,993,823 discloses using the lipopeptides to treat warm-blooded animals, including humans to elicit CTL

against viral or tumor proteins (see entire document, especially abstract, column 2 at lines 59-67, column 3-7 at line 18, column 46 at conclusion and claims).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have attached the multivalent auxiliary Th epitope taught by WO 95/19783 A1 via spacer as taught by WO 95/19783 A1 to lipopeptide of '746 or '564, to have used a hydrophilic spacer comprising either Lys or Arg as disclosed by US Patent No. 5,935,824 and by US 2003/0162719A1 (including the species of $CAAA(R)_7$, including minus the Cys residue, and including the Gly taught by WO 95/19783 A1 between the Th and the CTL epitope and in between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1 and to have made a vaccine.

The HIV CTL epitopes recited in claims 5 and 6 of '564 or '746 are obvious variants of the HIV epitopes recited in the instant claims, and the single lipid moieties recited in claims 7-9 of '564 or '746 are obvious variants of those recited in the instant claims, as per the disclosure of U.S. Patent No. 5,993,823 above.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to elicit an immune response or to improve efficacy of immunization to HIV, because WO 95/19783 A1 teaches attachment of a single lipid moiety can enhance the immune response to a CTL epitope, WO 95/19783 A1 teaches the use of a Th epitope in combination with a CTL epitope to enhance elicitation of the immune response, and that the elicitation of antibodies and Th cells is desirable in a vaccine composition, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, i.e., will be cleaved, US 2003/0162719A1 discloses that the transport of peptides such as class I and class II MCH antigens, i.e., CTL and HTL epitopes, respectively, across APC cell membranes is enhanced by attachment to polymers of basic subunits such as Arg, WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other. Claim 26 is included in this rejection because Gly and Arg are two amino acid residues from which the 2 to 10 amino acid residue linkers may be comprised.

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Group 1640
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March 28, 2005

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